

We claim:

1. A method for generating a mutation in a gene of interest comprising the steps of:

growing a hypermutable mammalian cell comprising the gene of interest and a dominant negative allele of a mismatch repair gene under control of an inducible transcriptional regulatory element;

testing the cell to determine whether the gene of interest harbors a mutation; and

restoring mismatch repair activity to the cell by decreasing expression of the dominant negative allele.

2. The method of claim 1 wherein the step of testing comprises analyzing a nucleotide sequence of the gene of interest.
3. The method of claim 1 wherein the step of testing comprises analyzing mRNA transcribed from the gene of interest.
4. The method of claim 1 wherein the step of testing comprises analyzing a protein encoded by the gene of interest.
5. The method of claim 1 wherein the step of testing comprises analyzing the phenotype of the cell.
6. The method of claim 1 wherein the mammalian cell is made by the process of introducing a polynucleotide comprising a dominant negative allele of a mismatch repair gene into a mammalian cell, whereby the cell becomes hypermutable.
7. The method of claim 6 wherein a reporter gene interrupted with a polymononucleotide tract which causes a reading frame-shift is introduced into the mammalian cell to permit the monitoring of hypermutability.

8. A method for generating a mutation in a mammal comprising the steps of:
- growing under inducing conditions one or more mammals comprising a dominant negative allele of a mismatch repair gene under control of an inducible transcriptional regulatory element;
 - selecting one or more mammals with a new trait acquired during the step of growing;
 - restoring genetic stability to the mammal by subjecting the mammal to non-inducing conditions.
9. The method of claim 8 wherein the new trait is identified by analyzing a nucleotide sequence.
10. The method of claim 8 wherein the new trait is identified by analyzing mRNA.
11. The method of claim 8 wherein the new trait is identified by analyzing a protein.
12. The method of claim 8 wherein the new trait is identified by analyzing a phenotype.
13. A transgenic mammal made by the method of claim 8.
14. The transgenic mammal of claim 13 wherein the mismatch repair gene is *PMS2*.
15. The transgenic mammal of claim 13 wherein the mismatch repair gene is human *PMS2*.
16. The transgenic mammal of claim 13 wherein the allele comprises a truncation mutation.
17. The transgenic mammal of claim 15 wherein the allele comprises a truncation mutation at codon 134 .
18. The transgenic mammal of claim 17 wherein the truncation mutation is a thymidine at nucleotide 424 of wild-type *PMS2*.
19. A method for generating a mutation in a gene of interest,

comprising the steps of:
growing under inducing conditions mammalian cells comprising (a)
a gene of interest and (b) a dominant negative allele of a mismatch repair gene
under control of an inducible regulatory element;

contacting the cells with a mutagen;

selecting one or more cells which comprise an altered gene, an
altered RNA, an altered polypeptide, or altered phenotypic trait.

20. The method of claim 19 further comprising the step of:
decreasing expression of the dominant negative allele in the selected
one or more cells by culturing in non-inducing conditions.

21. The method of claim 19 wherein expression of the dominant negative
allele is decreased by site directed mutagenesis of the dominant negative allele.

22. A method for generating a mutation in a gene of interest comprising the steps
of:

treating cells comprising (a) a gene of interest and (b) a genetic
defect in a mismatch repair gene with a mutagen;

selecting one or more cells which comprise an altered gene, RNA,
polypeptide or phenotypic trait.

23. The method of claim 22 wherein the genetic
defect in the mismatch repair gene is in PMS2.

24. The method of claim 22 wherein the genetic
defect in the mismatch repair gene is in PMS1.

25. The method of claim 22 wherein the genetic
defect in the mismatch repair gene is in MLH1.

26. The method of claim 22 wherein the genetic
defect in the mismatch repair gene is in MSH2.

27. The method of claim 22 wherein the genetic defect in the mismatch repair gene is in GTBP/MSH6.
28. The method of claim 22 wherein the genetic defect in the mismatch repair gene is in MSH3.
29. The method of claim 22 wherein the genetic defect is a dominant-negative mutation.
30. The method of claim 23 wherein the genetic defect is a dominant-negative mutation.
31. The method of claim 22 further comprising the step of:

introducing a complementing mismatch repair gene into the one or more selected cells whereby genetic stability is restored.

32. The method of claim 31 where the complementing mismatch repair gene is constitutively active in the one or more selected cells.
33. The method of claim 31 wherein the complementing mismatch repair gene is inducibly regulated.
34. The method of claim 31 wherein the complementing mismatch repair gene is in PMS2.
35. The method of claim 31 wherein the complementing mismatch repair gene is PMS1.
36. The method of claim 31 wherein the complementing mismatch repair gene is MLH1.
37. The method of claim 31 wherein the complementing mismatch repair gene is MSH2.

38. The method of claim 31 wherein the complementing mismatch repair gene is GTBP/MSH6.
39. The method of claim 31 wherein the complementing mismatch repair gene is MSH3.
40. The method of claim 31 wherein the complementing mismatch repair gene is introduced into the one or more selected cells by cell-cell fusion with a mismatch repair proficient cell.
41. A method for measuring mismatch repair activity of a cell comprising the step of:
assaying function of a gene in a cell wherein the gene comprises a polymononucleotide tract in its coding region which disrupts reading frame of the gene downstream of the polymononucleotide tract, wherein function of the gene correlates with reduced mismatch repair activity of the cell.
42. The method of claim 41 wherein a cell with a polymononucleotide tract in the gene which does not disrupt reading frame of the gene is used as a control.
43. The method of claim 41 wherein the cell is mismatch repair defective.
44. The method of claim 43 wherein a cell is used as a control which is mismatch repair proficient.
45. A mammal comprising a dominant negative allele of a mismatch repair gene under control of an inducible transcriptional regulatory element.
46. The mammal of claim 45 wherein the mismatch repair gene is *PMS2*.

47. The mammal of claim 45 wherein the mismatch repair gene is human *PMS2*.
48. The mammal of claim 45 wherein the allele comprises a truncation mutation.
49. The mammal of claim 48 wherein the allele comprises a truncation mutation at codon 134 .
50. The mammal of claim 49 wherein the truncation mutation is a thymidine at nucleotide 424 of wild-type *PMS2*.